

Exhibit E

ADVANCED ORGANIC CHEMISTRY

1906,

Structure

1906, Edition

Jerry March

ADVANCED ORGANIC CHEMISTRY

REACTIONS,
MECHANISMS, AND
STRUCTURE

FOURTH EDITION

Jerry March

Professor of Chemistry
Adelphi University



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An aldehyde or ketone is treated with an α -halo ester (e.g., α -halo ketones,⁴⁴³ α -halo N,N-disubstituted acids⁴⁴⁴ have also been used. With especially high reactivity can be achieved and with zinc and ultrasound.⁴⁴⁷ The use of zinc (e.g., In,⁴⁴⁸ Mn⁴⁴⁹) and Te,⁴⁵¹ and Bu₃Sb.⁴⁵² The aldehyde or ketone may contain various functional groups.

The reaction is analogous to the Grignard reaction and to RMgX. There is an

structure of which has been shown to be prepared from *t*-BuOCOCH₂Br and

t -Bu

of 32.

but sometimes (especially with aryl ketones) is an olefin. By the use of Bu₃P, making this an alternative to α -halo esters, α -halo ketones, not be formed from α -halo esters, reactions and yields are sometimes been carried out on nitriles.⁴⁵⁵

1975, 22, 423-460; Gaudemar *Organomet.*

56, 2659; Palomo; Aizpurua; López; Aurremunt. 1990, 20, 3277.
Huang; Chen; Shen *J. Chem. Soc., Perkin* 1985, 26, 4371.

1991, 21, 133.

75. See also Bortolussi; Seyden-Penne *Synth.*

Synth. Commun. 1988, 18, 453.

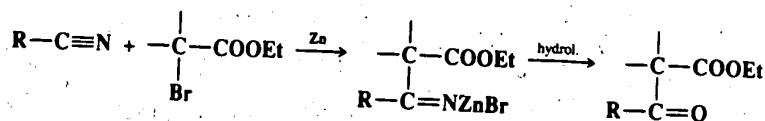
awamura; Inanaga; Yamaguchi *Tetrahedron*.

1984, 3, 1403.

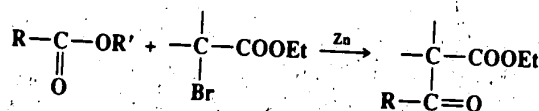
method. see Huang; Shi; Li; Wen *J. Chem.*

associated; Gaudemar *J. Organomet. Chem.*

REACTION 6-31

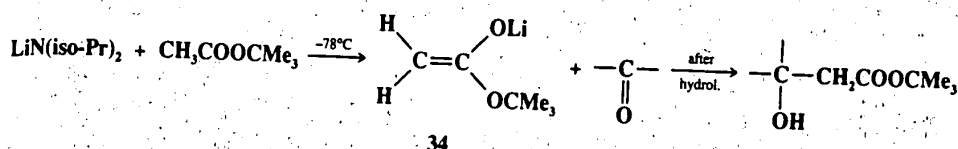


Carboxylic esters have also been used as substrates, but then, as might be expected (p. 881), the result is substitution and not addition:



The product in this case is the same as with the corresponding nitrile, though the pathways are different.

Addition of *t*-butyl acetate to lithium diisopropylamide (LDA) in hexane at -78°C gives the lithium salt of *t*-butyl acetate⁴⁵⁶ (2-22) as a stable solid. The nmr and ir spectra of this

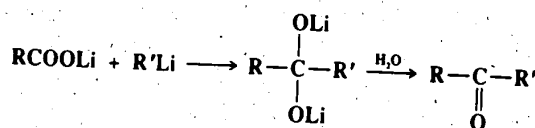


salt in benzene show it to have the enolate structure 34. Reaction of 34 with a ketone provides a simple rapid alternative to the Reformatsky reaction as a means of preparing β -hydroxy *t*-butyl esters. A similar reaction involves treatment of a ketone with a silyl ketene acetal $R_2C=C(OSiMe_3)OR'$ in the presence of TiCl₄⁴⁵⁷ (see also the reaction between silyl enol ethers and aldehydes and ketones, in 6-39).

OS III, 408; IV, 120, 444.

6-31. The Conversion of Carboxylic Acid Salts to Ketones with Organometallic Compounds

Alkyl-de-oxido-substitution



Good yields of ketones can often be obtained by treatment of the lithium salt of a carboxylic acid with an alkyl lithium reagent, followed by hydrolysis.⁴⁵⁸ R' may be aryl or primary, secondary, or tertiary alkyl. MeLi and PhLi have been employed most often. R may be

⁴⁵⁶Rathke; Sullivan *J. Am. Chem. Soc.* 1973, 95, 3050.

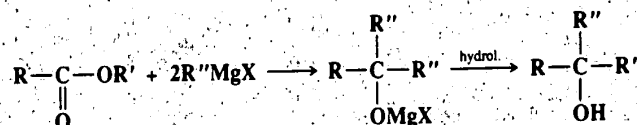
⁴⁵⁷See for example, Saigo; Osaki; Mukaiyama *Chem. Lett.* 1975, 989; Palazzi; Colombo; Gennari *Tetrahedron Lett.* 1986, 27, 1735; Oppolzer; Marco-Contelles *Helv. Chim. Acta* 1986, 69, 1699; Hara; Mukaiyama *Chem. Lett.* 1989, 1909. For a list of references, see Ref. 64, pp. 885-887. For methods of preparing silyl ketene acetals, see Revis; Hilty *Tetrahedron Lett.* 1987, 28, 4809, and references cited therein.

⁴⁵⁸For a review, see Jorgenson *Org. React.* 1970, 18, 1-97. For an improved procedure, see Rubottom; Kim *J. Org. Chem.* 1983, 48, 1550.

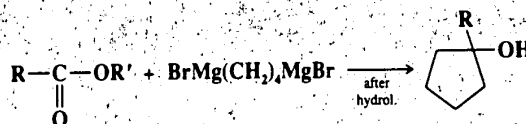
alkyl or aryl, though lithium acetate generally gives low yields. Tertiary alcohols are side products.

OS V, 775.

6-32 The Addition of Grignard Reagents to Acid Derivatives
Dialkyl, hydroxy-de-alkoxy, oxo-tersubstitution

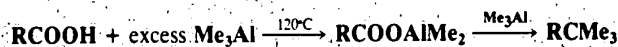


When carboxylic esters are treated with Grignard reagents, there is usually concomitant addition to the carbonyl (6-29) and substitution of R'' for OR' (0-104), so that tertiary alcohols are formed in which two R groups are the same. Formates give secondary alcohols and carbonates give tertiary alcohols in which all three R groups are the same: $(\text{EtO})_2\text{C}=\text{O} + \text{RMgX} \rightarrow \text{R}_3\text{COMgX}$. Acyl halides and anhydrides behave similarly, though these substrates are employed less often.⁴⁵⁹ There are many side reactions possible, especially when the acid derivative or the Grignard reagent is branched: enolizations, reductions (not for esters, but for halides), condensations, and cleavages, but the most important is simple substitution (0-104), which in some cases can be made to predominate. When 1,4-dimagnesium compounds are used, carboxylic esters are converted to cyclopentanol.⁴⁶⁰

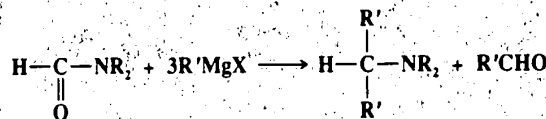


1,5-Dimagnesium compounds give cyclohexanols, but in lower yields.⁴⁶⁰

Trimethylaluminum, which exhaustively methylates ketones (6-29), also exhaustively methylates carboxylic acids to give *t*-butyl compounds⁴⁶¹ (see also 0-90):



Disubstituted formamides can give addition of 2 moles of Grignard reagent. The products of this reaction (called *Bouveault reaction*) are an aldehyde and a tertiary amine.⁴⁶² The use



of an amide other than a formamide can give a ketone instead of an aldehyde, but yields are generally low. It has proven possible to add two different R groups by sequential addition

⁴⁵⁹For a review of these reactions, see Kharasch; Reinmuth, Ref. 351, pp. 549-766, 846-869.

⁴⁶⁰Canonne; Bernatchez *J. Org. Chem.* 1986, 51, 2147; 1987, 52, 4025.

⁴⁶¹Meisters; Mole *Aust. J. Chem.* 1974, 27, 1665.

⁴⁶²For a review, see Ref. 176, pp. 59-63.